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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
SHIRLEY LONGACRE-ANDRE, ET AL.	: EXAMINER: J. L. GRUN
SERIAL NO: 09/134,333	:
FILED: AUGUST 14, 1998	: GROUP ART UNIT: 1641

FOR: RECOMBINANT PROTEIN CONTAINING A C-TERMINAL FRAGMENT OF PLASMODIUM MSP-1

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an appeal from the Final Rejection of the claims dated December 15, 2008.

I. REAL PARTY IN INTEREST

The real party in interest is Institute Pasteur of Paris, France, and New York University of New York, New York, by virtue of the assignment recorded at Reel/Frame 009862, frame 0784.

II. RELATED APPEALS AND INTERFERENCES

Appellants, Appellants' legal representative and their assignee are not aware of any appeals or interferences which will directly affect or be directly affected by or having a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 134, 139-142, 145 and 148-155, 157, 158, 160, 161, 163, 164 and 166-177 are pending and are the subject of this appeal.

IV. STATUS OF AMENDMENTS

An Amendment and Request for Reconsideration was filed on June 15, 2009. As indicated by the Advisory Action dated June 25, 2009, that Amendment has been entered, along with an indication that the rejection of the claims under 35 U.S.C §112, second paragraph is withdrawn.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

As set forth in Claim 134, the present invention relates to a vaccinating composition against a *Plasmodium* parasite which is infectious in man {see the specification at page 4, lines 16-17}, comprising as an active principle a recombinant protein {see the specification at page 4, lines 11-19} whose polypeptide sequence comprises:

a) a 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium* parasite that is infectious in man {see the specification at page 4, lines 20-22}, other than *Plasmodium vivax* {see the specification at page 12, line 7}; which induces an immune response and which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite {see the specification at page 4, lines 25-27}; wherein said C-terminal fragment remains anchored via a glycosylphosphatidylinositol group to the surface of said *Plasmodium* parasite at an end of its penetration phase into human erythrocytes during an infectious cycle and wherein said recombinant protein comprises conformational epitopes {see the specification at page 4, lines

22-24}, which are contained in two epidermal growth factor regions {see the specification at page 9, lines 19-20} and is unstable in a reducing agent {see the specification at page 5, line 2}, wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) has atomic coordinates in Annexes I or III; and NMR fingerprints of Figures 12.0a to 12.0c or 12.2a to 12.2c {see the specification at page 35, line 19 and page 37, line 27 to page 38, line 2}; and

b) alum {see the specification at page 26, line 17},

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 24, line 1 to page 25, line 5}.

As set forth in Claim 145, the present invention also relates to a vaccinating composition against a *Plasmodium* parasite which is infectious in man {see the specification at page 4, lines 16-17}, comprising as a active principle a recombinant protein {see the specification at page 4, lines 11-19} whose polypeptide sequence comprises:

a) 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium cynomolgi* parasite that is infectious in man {see the specification at page 4, lines 20-22}, and wherein said recombinant protein comprises conformational epitopes {see the specification at page 9, lines 19-20}, which are contained in two epidermal growth factor regions and is unstable in a reducing agent {see the specification at page 9, lines 19-20 and page 5, line 2}; and

b) alum {see the specification at page 26, line 17},

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 24, line 1 to page 25, line 5}.

As set forth in Claim 151, the present invention relates to a recombinant protein {see the specification at page 4, lines 11-19} whose polypeptide sequence comprises:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met_1 to Asp_{32} {see the specification at page 16, lines 9-11}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium falciparum* consisting of an amino acid sequence from Asn at amino acid position 3 to Ser at amino acid position 95 of SEQ ID NO: 1 {see the specification at page 16, line 15} which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 4, lines 25-27}.

As set forth in Claim 152, the present invention also relates to a recombinant protein {see the specification at page 4, lines 11-19} whose polypeptide sequence comprises:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met_1 to Asp_{32} {see the specification at page 16, lines 9-11}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium falciparum* consisting of an amino acid sequence from Asn at amino acid position 3 to Ile at amino acid position 116 of SEQ ID NO: 4 {see the specification at page 17, lines 9-14} which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 4, lines 25-27}.

As set forth in Claim 153, the present invention also relates to a recombinant protein {see the specification at page 4, lines 11-19} whose polypeptide sequence consists of:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met_1 to Asp_{32} {see the specification at page 16, lines 9-11}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium cynomolgi* consisting of an amino acid sequence from Lys_{276} to Ser_{380} as shown in SEQ ID NO: 11 which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 4, lines 25-27}, and wherein the fragment has atomic coordinates in AnnexI; and NMR fingerprints of Figures 12.0 a to 12.0c {see the specification at page 35, line 19 and page 37, line 27 to page 38, line 2}.

As set forth in Claim 176, the present invention also relates to a vaccinating composition against a *Plasmodium* parasite which is infectious in man {see the specification at page 4, lines 16-17}, comprising as an active principle a recombinant protein {see the specification at page 4, lines 11-19} whose polypeptide sequence comprises:

a) 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium* parasite that is infectious in man {see the specification at page 4, lines 20-22}, other than *Plasmodium vivax* {see the specification at page 12, line 7}; which induces an immune response and which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite {see the specification at page 4, lines 25-27}; wherein said C-terminal fragment remains anchored to the surface of said *Plasmodium* parasite at an end of its penetration phase into human erythrocytes during an infectious cycle {see the specification at page 60, lines 7-9}, wherein said recombinant protein comprises conformational epitopes {see the specification at page 9, lines 19-20}, which are contained in two epidermal growth factor regions and is unstable in a reducing agent {see the specification at page 9, lines 19-20 and page 5, line 2} and further comprises

upstream of said 19 kilodalton (p19) C-terminal fragment, a polypeptide containing less than 50 amino acids of a C-terminal end of p33 of a MSP-1 protein of a *Plasmodium* parasite {see the specification at page 8, line 21 to page 9, lines 15}; and

b) alum {see the specification at page 26, line 17},

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 24, line 1 to page 25, line 5}.

As set forth in Claim 177, the present invention also relates to a vaccinating composition against a *Plasmodium* parasite which is infectious in man {see the specification at page 4, lines 20-22}, comprising as an active principle an oligomer of a recombinant protein {see the specification at page 14, lines 23-26} whose polypeptide sequence comprises:

a) a 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium* parasite that is infectious in man {see the specification at page 4, lines 16-17}, other than *Plasmodium vivax* {see the specification at page 12, line 7}; which induces an immune response and which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite {see the specification at page 24, line 1 to page 25, line 5}; wherein said C-terminal fragment remains anchored to the surface of said *Plasmodium* parasite at an end of its penetration phase into human erythrocytes during an infectious cycle and wherein said recombinant protein comprises conformational epitopes {see the specification at page 9, lines 19-20}, which are contained in two epidermal growth factor regions and is unstable in a reducing agent (see the specification at page 5, line 2), wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) has atomic coordinates in Annexes I or III; and NMR

fingerprints of Figures 12.0a to 12.0c or 12.2a to 12.2c {see the specification at page 35, line 19 and page 37, line 27 to page 38, line 2}; and

b) alum {see the specification at page 26, line 17 },

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite {see the specification at page 24, line 1 to page 25, line 5}.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 153, 169, 172 and 175 are unpatetnable under 35 U.S.C. § 103(a) over Longacre (1995) in view of Longacre et al. (1994).

2. Whether Claims 134, 139 to 141, 145, 148 to 150, 176 and 177 are unpatentable under 35 U.S.C. § 103(a) over Longacre (1995) in view of Longacre et al. (1994) and further in view of Holder et al. (U.S. 5,720,959).

3. Whether Claims 151, 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173 and 174 are unpatentable under 35 U.S.C. § 103(a) over the combined teachings of Chappel and Holder, Miller et al., Longacre et al. (1994) and Longacre (1995).

4. Whether Claims 134, 139 to 142, 148, 150, 176 and 177 are unpatentable under 35 U.S.C. § 103(a) over Chappel et al., Miller et al. and Longacre (1994) in view of Longacre et al. (1995) and further in view of Holder et al.

VII. ARGUMENT

1. Claims 153, 169, 172 and 175 are not obvious under 35 U.S.C. § 103(a) over Longacre (1995) in view of Longacre et al. (1994).

Longacre (1995) disclose the C-terminal sequence of a *Plasmodium cynomolgi* MSP-1 and its homology with other *Plasmodium* species. This reference does not disclose that the amino acid sequence from Lys_{296} to Ser_{380} as shown in SEQ ID NO:11 induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

Longacre et al. (1994) disclose recombinant proteins from *Plasmodium vivax* merozoite surface protein that have been produced in a baculovirus expression system. 42-kDA and a 19 kDA proteins were recombinantly produced, which were N-glycosylated.

Longacre et al. (1994) does not disclose or suggest that the recombinant constructs produced therein can induce an immune response, which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite. Rather, immunoblotting with a pool of immune human sera obtained by donors living in a *P. Vivax* hyperendemic region of Sri Lanka was used to only confirm that the recombinant proteins of 42 kDA and 19 kDA were recombinantly produced. However, this data is no indication that parasitemia can be inhibited *in vivo*.

Indeed, the Arnot et al. article of record demonstrates that baculovirus MSP-1_{19} gave superior results compared with other antigen-based malaria vaccine candidates. Baculovirus produced MSP-1_{19} immunizations produce the highest parasite-specific antibody titers in immunofluorescence assays; induced more antibodies, in ELISAs, gave the highest levels of growth inhibitor in HB3 and 3D7 parasite cultures and inhibited growth as well as or better at lower IgG concentrations. This is an unexpected result, not set forth in the cited references, and should be considered with respect to the obviousness rejection.

Moreover, neither of these two cited references suggests that the recombinant protein in Claim 153 can form oligomers when recombinantly produced, which oligomers can inhibit parasitemia *in vivo*. In addition, 2 to 50 monomer units are not suggested by the cited references.

In fact due to the unpredictability in this art the mere production of recombinant proteins and oligomers thereof cannot be equated with their physiologic action *in vivo* unless truly demonstrated. It is only in the present specification that it was scientifically proven that the recombinant constructs set forth in the rejected claims that the recombinant construct set forth in Claim 153, as well as the oligomers thereof can inhibit parasitemia *in vivo*.

Moreover, since Claim 153 is not obvious then conjugation to a carrier should not be obvious.

In view of the foregoing, this rejection is unsustainable.

2. Claims 134, 139 to 141, 145, 148 to 150, 176 and 177 are not obvious under 35 U.S.C. § 103(a) as being unpatentable over Longacre (1995) in view of Longacre et al. (1994) and further in view of Holder et al. (U.S. 5,720,959).

Longacre et al. (1995) and Longacre et al. (1994) were discussed extensively above and the argument applies with respect to this rejection as well. It should be noted that neither reference suggests a vaccinating composition in which parasitemia can be inhibited *in vivo*. Moreover Longacre et al. (1995) merely discloses a sequence comparison of various *Plasmodium* species and does not disclose or suggest the production of recombinant proteins that can be used in a vaccinating composition. Longacre et al. (1994) discloses several recombinantly produced *Plasmodium vivax* MSP-1 C-terminal recombinant proteins. The rejected claims exclude any a 19 kDa C-terminal fragment MSP-1 protein from *Plasmodium*

vivax. Moreover, there is no suggestion in Longacre et al (1994) to use in a vaccinating composition an anchored C-terminal. 19 kDA MSP-1 protein.

Holder et al. does not remedy the deficiencies of the primary references. U.S. patent 5,720,959 discloses recombinantly produced polypeptides having EGF-1 and EGF-2 domains. The EGF-1 domain has 48 amino acids, while the EGF-2 domain has 53 amino acids. These domains were recombinantly produced as fusion proteins in *E. coli*. To demonstrate immunogenicity another recombinantly produced EGF-1 and EGF-2 from *Plasmodium yoelii* was recombinantly produced also in *E. coli* and mice were immunized with the fusion protein GST containing EGF-1 and EGF-2 domains, as well as the recombinantly produced EGF-1 and EGF-2 domains cleaved from the fusion protein.

The mice immunized with the recombinantly produced EGF-domains in *E. coli* had little or no parasitemia after 17 days. The conclusion was that by producing EGF-like domains in *E. coli* the disulphide bonds and tertiary structure of these domains was conserved.

First of all, the claimed invention is not directed to *Plasmodium* parasites that are derived from mice. Rather the claims recite that the 19 kDa C-terminal MSP-1 protein is from a "*Plasmodium* parasite **that is infectious in man**."

Secondly, none of the recombinantly produced EGF-domains produced in *E. coli* from the *Plasmodium falciparum* clones T9/96 and T9/94 were tested for immunogenicity.

Hence the only conclusion that the skilled artisan can draw from the teachings of Holder et al. is that EGF-1 and EGF-2 domains from *P. yoelii* recombinantly produced in *E. coli* in which mice were immunized therewith appear to be protected against parasitemia for 17 days. These results cannot be equated to mean that the other constructs from *Plasmodium falciparum* induce the same results, since these EGF-domains were never used to test for immunogenicity.

Thus there is simply no suggestion or even teaching that a *Plasmodium* parasite that is infectious in man other than *Plasmodium vivax* can induce an immune response and inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite. Without such, demonstration in any of the cited references, or a suggestion from the combination thereof, this rejection cannot be maintained..

Finally, as set forth above unexpected results are achieved with baculovirus produced MSP-1_{19}, which must be considered with respect to obviousness and the teaching of prior art.

In view of the foregoing, this rejection is unsustainable.

3. Claims 151, 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173 and 174 are not obvious under 35 U.S.C. § 103(a) over the combined teachings of Chappel and Holder, Miller et al., Longacre et al. (1994) and Longacre (1995).

The rejected claims are directed to specific recombinant proteins, as well as oligomers thereof.

Chappel and Holder disclose that monoclonal antibodies that inhibit *Plasmodium falciparum* invasion in vitro recognize the EGF-1 domain of MSP-1. The Examiner relies on the disclosure of S42ΔA, which contains 271 amino acids of MSP-1 from the Wellcome strain, including both EGF domains, fused to the N-terminal 34 amino acids of MSP-1, also from the Wellcome strain. There is no suggestion in Chappel and Holder to use another leader sequence from a different *Plasmodium* species or to limit this leader sequence to 32 amino acids. Nor is there any suggestion in this reference to construct a recombinant C-terminal MSP-1 protein that has less than 271 amino acids.

Furthermore, Chappel and Holder fail to suggest that their recombinant proteins recited therein have the ability to induce an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite. At best their conclusion of their study was speculative, as evidenced by the following statement at page 309:

> In conclusion, we have shown that the first EGF-like domain can be expressed as a fusion protein in *E. coli* and it binds growth-inhibitory antibodies; if it is possible to stimulate a strong immune response to, this polypeptide, it has potential for development into a vaccine against blood-stage malaria.

Thus, the only conclusion that can be made by the disclosure of Chappel and Holder is that the first EGF-1 domain binds growth-inhibitory antibodies. This domain was not proven at all to induce an immune response that can inhibit parasitemia *in vivo*.

Miller et al. was only cited to orient the sequences in Chappel and Holder.

Longacre et al. (1994) is directed to *Plasmodium vivax* recombinant MSP-1 proteins wherein the leader sequence and the C-terminal fragment is from *Plasmodium vivax*. There is no suggestion in this reference to interchange a different *Plasmodium* species in the C-terminal MSP-1 fragment.

Longacre (1995) compares the C-terminal MSP-1 sequences of *P. cynomolgi* with different strains of *P. vivax*. The sequence of *P. falciparum* is not disclosed in this reference.

In fact the two cited Longacre references have no disclosure or suggestion of using a *P. falciparurn* recombinant protein.

The combination of these references fails to suggest to the skilled artisan the recombinantly claimed constructs cited in this rejection, which can induce an immune response that can inhibit parasitemia *in vivo*.

As set forth above and described in Arnot et al., unexpected results of enhanced parasite-specific antibody titers, a larger induction of antibodies and higher levels of growth inhibition were achieved with baculovirus produced MSP-1_{19}, which is an unexpected result not foreseen in the cited prior art.

Due to the unpredictability in this art, without such a showing this rejection cannot be maintained.

4. Claims 134, 139 to 142, 148, 150, 176 and 177 are not obvious under 35 U.S.C. § 103(a) as being unpatentable over Chappel et al., Miller et al. and Longacre (1994) in view of Longacre et al. (1995) and further in view of Holder et al.

Chappel et al., Miller et al. and Longacre (1994) in view of Longacre et al. were discussed extensively above and these arguments apply to this rejection as well. None of these cited references suggest to the skilled artisan the recombinantly claimed constructs can induce an immune response that can inhibit parasitemia *in vivo*. Since this art is unpredictable proper experimental results must be proven, and not merely hypothesized.

Although the U.S. patent to Holder et al. does demonstrate that recombinant constructs producing EGF-1 and EGF-2 domains from *P. yoelii* stimulate a protective immune response in mice no demonstration was made that the recombinant EGF-domain constructs directed towards *P. falciparum* attain the same protection in primates.

The combination of these references fails to suggest to the skilled artisan the recombinantly claimed constructs cited in this rejection, which can induce an immune response that can inhibit parasitemia *in vivo* in a host transfected with a *Plasmodium* parasite and wherein said *Plasmodium* parasite is infectious in man.

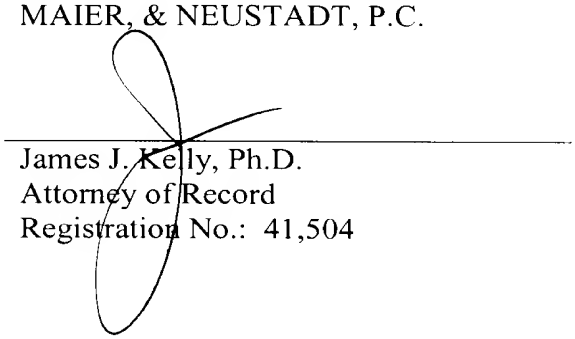
As set forth above and described in Arnot et al., unexpected results of enhanced parasite-specific antibody titers, a larger induction of antibodies and higher levels of growth inhibition were achieved with baculovirus produced MSP-1_{19}, which is an unexpected result not foreseen in the cited prior art.

In view of the foregoing, this rejection is unsustainable.

Reversal of the Examiner's rejections is requested.

Respectfully Submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER, & NEUSTADT, P.C.



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CLAIMS APPENDIX

Claims 134, 139-142, 145 and 149-155, 157, 158, 160, 161, 163, 164 and 166-177 are under appeal and read as follows:

134. A vaccinating composition against a *Plasmodium* parasite which is infectious in man, comprising as an active principle a recombinant protein whose polypeptide sequence comprises:

a) a 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium* parasite that is infectious in man, other than *Plasmodium vivax;* which induces an immune response and which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite; wherein said C-terminal fragment remains anchored via a glycosylphosphatidylinositol group to the surface of said *Plasmodium* parasite at an end of its penetration phase into human erythrocytes during an infectious cycle and wherein said recombinant protein comprises conformational epitopes, which are contained in two epidermal growth factor regions and is unstable in a reducing agent, wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) has atomic coordinates in Annexes I or III; and NMR fingerprints of Figures 12.0a to 12.0c or 12.2a to 12.2c ; and

b) alum,

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

139. The vaccinating composition of Claim 134, wherein said recombinant protein further comprises, upstream of said 19 kilodalton (p19) C-terminal fragment, a polypeptide

containing less than 50 amino acids of a C-terminal end of p33 of a MSP-1 protein of a *Plasmodium* parasite.

140. The vaccinating composition of Claim 139, wherein said C-terminal end of p33 is obtained from a cleavage of p42 of a same MSP-1 protein of a *Plasmodium* parasite.

141. The vaccinating composition of Claim 139, wherein said polypeptide contains less than 35 amino acids.

142. The vaccinating composition of Claim 140, wherein said C-terminal end of p33 is that end that is conserved in *P. falciparum*.

145. A vaccinating composition against a *Plasmodium* parasite which is infectious in man, comprising as a active principle a recombinant protein whose polypeptide sequence comprises:

a) 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium cynomolgi* parasite that is infectious in man, and wherein said recombinant protein comprises conformational epitopes, which are contained in two epidermal growth factor regions and is unstable in a reducing agent; and

b) alum,

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

148. The vaccinating composition of Claim 134, wherein said recombinant protein is conjugated to a carrier molecule.

149. The vaccinating composition of Claim 145, wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein I of the merozoite form (MSP-1 protein) has the atomic coordinates in Annex I; and the NMR fingerprints of Figures 12.0a to 12.0c.

150. The vaccinating composition of Claim 145, which is hydrosoluble.

151. A recombinant protein whose polypeptide sequence comprises:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met_1 to Asp_{32}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium falciparum* consisting of an amino acid sequence from Asn at amino acid position 3 to Ser at amino acid position 95 of SEQ ID NO: 1 which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

152. A recombinant protein whose polypeptide sequence comprises:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met_1 to Asp_{32}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium falciparum* consisting of an amino acid sequence from Asn at amino acid position 3 to Ile at amino acid position 116 of SEQ ID NO: 4 which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

153. A recombinant protein whose polypeptide sequence consists of:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met_1 to Asp_{32}; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium cynomolgi* consisting of an amino acid sequence from Lys_{276} to Ser_{380} as shown in SEQ ID NO: 11 which fragment induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite, and wherein the fragment has atomic coordinates in AnnexI; and NMR fingerprints of Figures 12.0 a to 12.0c.

154. The recombinant protein of Claim 151, wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) has atomic coordinates in Annex III; and NMR fingerprints of Figures 12.2a to 12.2c.

155. The recombinant protein of Claim 152, wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) has atomic coordinates in Annex III; and NMR fingerprints of Figures 12.2a to 12.2c.

157. The recombinant protein of Claim 151, which further comprises, upstream of said 19 kilodalton (p19) C-terminal fragment, a polypeptide containing less than 50 amino acids of a C-terminal end of p33 from a MSP-1 protein of a *Plasmodium* parasite.

158. The recombinant protein of Claim 152, which further comprises, upstream of said 19 kilodalton (p19) C-terminal fragment, a polypeptide containing less than 50 amino acids of a C-terminal end of p33 from a MSP-1 protein of a Plasmodium parasite.

160. The recombinant protein of Claim 157, wherein said C-terminal end of p33 is obtained from a cleavage of p42 of a same MSP-1 protein of a *Plasmodium* parasite.

161. The recombinant protein of Claim 158, wherein said C-terminal end of p33 from a cleavage of p42 of a same MSP-1 protein of a *Plasmodium* parasite.

163. The recombinant protein of Claim 157, wherein said polypeptide contains less than 35 amino acid residues.

164. The recombinant protein of Claim 158, wherein said polypeptide contains less than 35 amino acid residues.

166. The recombinant protein of Claim 152, wherein said 19 kilodalton C-terminal fragment remains anchored to the surface of said *Plasmodium* parasite via a glycosylphosphatidylinositol group.

167. An oligomer of the recombinant protein of Claim 151.

168. An oligomer of the recombinant protein of Claim 152.

169. An oligomer of the recombinant protein of Claim 153.

170. The oligomer of Claim 167, wherein said oligomer comprises from 2 to 50 monomer units of a sequence of said recombinant protein.

171. The oligomer of Claim 168, wherein said oligomer comprises from 2 to 50 monomer units of a sequence of said recombinant protein.

172. The oligomer of Claim 169, wherein said oligomer comprises from 2 to 50 monomer units of a sequence of said recombinant protein.

173. The recombinant protein of Claim 151, which is conjugated to a carrier molecule.

174. The recombinant protein of Claim 152, which is conjugated to a carrier molecule.

175. The recombinant protein of Claim 153, which is conjugated to a carrier molecule.

176. A vaccinating composition against a *Plasmodium* parasite which is infectious in man, comprising as an active principle a recombinant protein whose polypeptide sequence comprises:

a) 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium* parasite that is infectious in man, other than *Plasmodium vivax;* which induces an immune response and which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite; wherein said C-terminal fragment remains anchored to the surface of said *Plasmodium* parasite at an end of its penetration phase into human erythrocytes during an infectious cycle, wherein said recombinant protein

comprises conformational epitopes, which are contained in two epidermal growth factor regions and is unstable in a reducing agent and further comprises upstream of said 19 kilodalton (p19) C-terminal fragment, a polypeptide containing less than 50 amino acids of a C-terminal end of p33 of a MSP-1 protein of a *Plasmodium* parasite; and

b) alum,

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

177. A vaccinating composition against a *Plasmodium* parasite which is infectious in man, comprising as an active principle an oligomer of a recombinant protein whose polypeptide sequence comprises:

a) a 19 kilodalton (p19) C-terminal fragment of a surface protein 1 of a merozoite form (MSP-1 protein) of a *Plasmodium* parasite that is infectious in man, other than *Plasmodium vivax;* which induces an immune response and which can inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite; wherein said C-terminal fragment remains anchored to the surface of said *Plasmodium* parasite at an end of its penetration phase into human erythrocytes during an infectious cycle and wherein said recombinant protein comprises conformational epitopes, which are contained in two epidermal growth factor regions and is unstable in a reducing agent, wherein said 19 kilodalton (p19) C-terminal fragment of the surface protein 1 of the merozoite form (MSP-1 protein) has atomic coordinates in Annexes I or III; and NMR fingerprints of Figures 12.0a to 12.0c or 12.2a to 12.2c ; and

b) alum,

wherein said vaccinating composition induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

EVIDENCE APPENDIX

Arnot et al., *Clinical and Vaccine Immunology*, Sept. 2008, pp. 1345-1355, submitted with the Amendment and Request for Reconsideration filed on June 15, 2009.

Rule 132 Declaration of Shirley Longacre, submitted on June 16, 2006. This Declaration establishes that *P. yoelii* is a rodent malaria parasite and is not infectious in man; that proteins expressed in *E. coli* do not form correct disulphide bonds even when expressed as fusion proteins; and the unpredictability of vaccine compositions which are not tested for immunogenicity.

RELATED PROCEEDINGS APPENDIX

None.